Autoantibodies in Sjögren’s syndrome: Clinical presentation and regulatory mechanisms

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Summary

Primary Sjögren’s syndrome (pSS) is a systemic autoimmune disease mostly affecting the exocrine glands. A large number of autoantibodies have been detected in the serum of patients with pSS. Among them, anti-Ro/SSA and anti-La/SSB autoantibodies are the most common; they serve as disease markers and are involved in the pathogenesis of neonatal lupus syndrome (NLS). Other autoantibodies are associated with significant clinical phenotypes, such as cryoglobulins with development of non-Hodgkin’s lymphoma, anti-centromere antibodies with Raynaud’s phenomenon and anti-mitochondrial antibodies with liver pathology. As a result, pSS patients can be schematically categorized in subgroups according to their serological profile. Although the clinical utility of these autoantibodies is appreciated, little is known about the mechanisms related to their production and the regulation of the autoimmune response. In the present review, the clinical subsets of patients with pSS related to different autoantibodies as well as the regulating mechanisms of their production with special emphasis on idiotypic/anti-idiotypic network are discussed.

Primary Sjögren’s syndrome (pSS) or autoimmune epithelitis [1] is a prototype of chronic systemic autoimmune diseases characterized by lymphocytic infiltration of the exocrine glands and circulating autoantibodies binding on a plethora of organ and non-organ specific autoantigens [2]. During the last decade, particular clinical associations have been delineated for each of the autoantibodies detected in the pSS patients’ sera, while their utility in establishing diagnosis, classification and prognosis has been proved significant. However, it is still unknown whether any of these autoantibodies have a direct pathogenetic role for autoantibody-mediated injury, contribute to tissue lesion or they just constitute an epiphenomenon in the context of a non-specific autoimmune response to salivary glands. It is noteworthy that anti-Ro/SSA and anti-La/SSB antibodies, which are considered to be the most typical among the pSS autoantibodies and
are included in the European-American Consensus Group classification criteria [3], seem to be involved in the local autoimmune response-taking place in the affected exocrine glands [4,5].

Much effort has been made on clarifying the potential mechanisms involved in the production of autoantibodies and the regulation of the autoimmune response. This could provide us useful information regarding the initiation and perpetuation of the dysregulated immune response. In particular, it has been speculated that the autoimmune response is antigen-driven and that it is regulated by factors either extrinsic or intrinsic to the immune system [6]. In this regard, the putative impact of idiotypic/anti-idiotypic network on the regulation of autoantibodies response has been the subject of recent research.

### Clinical presentation

PSS sera contain a variety of autoantibodies that can be arbitrarily categorized into three groups:
- autoantibodies serving as disease markers;
- autoantibodies associated with significant clinical phenotypes;
- autoantibodies exhibiting possible pathogenetic role (Table I). The molecular characteristics of the involved autoantigens are summarized in Table II.

### Autoantibodies serving as disease markers

#### Anti-Ro/SSA and anti-La/SSB antibodies

Antinuclear antibodies (ANA) are found positive in approximately 77 to 90% of pSS patients when detected by indirect immunofluorescence (IIF) on Hep-2 cells [7–11], exhibiting usually a fine speckled pattern (figure 1a) [12]. Among them, the most common and typical in patients with pSS are those directed against the autoantigens Ro/SSA and La/SSB. The Ro/La ribonucleoprotein complexes are protein-RNA complexes

#### Table I

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#### Definition

- **ANA**: Antinuclear antibodies
- **AMA**: Anti-mitochondrial antibodies
- **ASMA**: Anti-smooth muscle antibodies
- **ANA**: Antinuclear antibodies
- **Anti-CCP**: Anti-cyclic citrullinated peptide antibodies
- **CA**: Carbonic anhydrase
- **CHB**: Congenital heart block
- **ELISA**: Enzyme-linked immunosorbent assay
- **IIF**: Indirect immunofluorescence
- **IVIG**: Intravenous Immunoglobulin
- **M3R**: M3-muscarinic receptor
- **MRs**: Muscarinic receptors
- **NLS**: Neonatal lupus syndrome
- **PBC**: Primary biliary cirrhosis
- **pSS**: Primary Sjögren’s syndrome
- **RA**: Rheumatoid arthritis
- **RF**: Rheumatoid factor
- **SS**: Sjögren’s Syndrome

#### Glossary

- **ACA**: anti-centromere antibodies
- **AMA**: anti-mitochondrial antibodies
- **ASMA**: anti-smooth muscle antibodies
- **ANA**: Antinuclear antibodies
- **Anti-CCP**: anti-cyclic citrullinated peptide antibodies
- **CA**: carbonic anhydrase
- **CHB**: congenital heart block
- **ELISA**: enzyme linked immunosorbent assay
- **IIF**: indirect immunofluorescence
- **IVIG**: intravenous immunoglobulin
- **M3R**: M3-muscarinic receptor
- **MRs**: muscarinic receptors
- **NLS**: neonatal lupus syndrome
- **PBC**: primary biliary cirrhosis
- **pSS**: primary Sjögren’s syndrome
- **RA**: rheumatoid arthritis
- **RF**: rheumatoid factor
- **SS**: Sjögren’s Syndrome
formed by the association of the Ro52 kDa, Ro60 kDa and La proteins with small cytoplasmic RNA (hsyRNA) [13]. The localization of these proteins is intracellular [14] and therefore they are inaccessible to the immune system. In order for them to be translocated to the cell surface and thus become immunogenic, some specific mechanisms, such as apoptosis and exosomes, are required [15,16].

A variety of methods have been used for the detection of anti-Ro/SSA and anti-La/SSB antibodies. Although RNA precipitation is considered to be the gold standard method, other techniques, such as counter-immunoelectrophoresis, immunodiffusion and enzyme linked immunosorbent assay (ELISA) are more commonly utilized in everyday routine analysis [17]. Depending on the method applied for their identification, anti-Ro/SSA and anti-La/SSB antibodies are detected in approximately 50 to 70% of pSS patients [18]. Interestingly, anti-Ro/SSA antibodies may be found either solely or concomitantly

<table>
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<td>CENP-B</td>
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1 Predicted on the basis of the amino acid sequence.
with anti-La/SSB antibodies, whereas exclusive anti-La/SSB positivity is rare [19].
As already mentioned, these autoantibodies form an independent item of the American-European Consensus Group classification criteria and their detection in patients with suspected pSS strongly supports the diagnosis [3]. The Ro/La antibody profile that is presented at the diagnosis of pSS seems to remain constant throughout the course of the disease [20], even after the administration of B-cell depletion therapy with rituximab [21].
In patients with pSS, anti-Ro/SSA and anti-La/SSB antibodies have been correlated with younger age at diagnosis, longer disease duration, more severe dysfunction of the exocrine glands, recurrent parotid gland enlargement and higher intensity of the lymphocytic infiltrates invading the minor salivary glands [22,23]. There are also studies suggesting a higher prevalence of extraglandular manifestations in pSS patients positive for anti-Ro/La antibodies [24,25], including splenomegaly, lymphadenopathy, vasculitis and Raynaud’s phenomenon. Additionally, these autoantibodies can also be found in patients with rheumatoid factor (RF), polyclonal hypergamma-globulinemia and cryoglobulinemia [8,25].

Autoantibodies associated with significant clinical phenotypes

Rheumatoid factors and cryoglobulins
The prevalence of RF and cryoglobulins in pSS patients is ~40 to 50% and ~10 to 15%, respectively [9,25–27]. Both have been correlated with younger age, extraglandular manifestations and positivity for other serological markers [28]. Particularly, the presence of cryoglobulins, and mostly of type II containing an IgMκ RF, defines a clinical subset of pSS with poor prognosis, as they have been recognised as risk factors for lymphoma development and death [7,27–30].

Anti-centromere antibodies
Anti-centromere antibodies (ACA) are found in patients with limited cutaneous sclerosis (lcSSc) and their prevalence in pSS ranges from 4 to 17% [31–34], when detected by IIF (figure 1b). The pSS patients with ACA are more likely to develop Raynaud’s phenomenon, exhibit a higher mean age at disease onset and they are less likely to have anti-Ro/SSA and anti-La/SSB antibodies, positive RF, leukocytopenia and hypergammaglobulinemia [31–33,35,36]. Additionally, ACA (+) pSS patients present calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia less frequently as compared to ACA (+) SSC patients [32]. It has been proposed that these autoantibodies may characterize a subset of patients with a clinical phenotype intermediate between primary SS and systemic sclerosis. An additional interesting aspect has been shown by several studies revealing a tendency for progression of ACA positive pSS patients to overt systemic sclerosis [31–33,37].

Anti-mitochondrial and anti-smooth muscle antibodies
Anti-mitochondrial antibodies (AMA) consist a diagnostic marker for primary biliary cirrhosis (PBC) [38]. The prevalence of AMA (figure 1c) in pSS patients is 5 to 6.5% [39,40]. Taken the association between pSS and PBC [41], further studies have proposed AMA as a sensitive indicator of liver involvement in pSS patients that predisposes them to develop autoimmune cholangitis similar to PBC [42]. On the other hand, anti-smooth muscle antibodies (ASMA) are recognized as the hallmark of type 1 autoimmune hepatitis, which seems to be a rare manifestation of pSS. Although ASMA may exist in pSS patients’ sera in a quite large proportion [10,43], this finding appears to have no clinical significance. However, some authors have indicated an association between ASMA positivity, particularly in high titres, and an underlying autoimmune disease of the liver [42,44,45].

**Figure 1**
Indirect immunofluorescence on Hep2-cells; a: antinuclear antibodies (ANA) presenting a fine speckled pattern; b: anti-centromere antibodies (ACA) and c: anti-mitochondrial antibodies (AMA).
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**Anti-cyclic citrullinated peptide antibodies**

Anti-cyclic citrullinated peptide antibodies (anti-CCP) are present in a small percentage (7–10%) of pSS patients [46–49] and have been correlated by some investigators with the development of non-erosive synovitis [48,50]. However, it should be noted that these reports do not elucidate whether the presence of anti-CCP antibodies is related to SS associated with rheumatoid arthritis (RA).

**Autoantibodies exhibiting possible pathogenetic role**

**Anti-Ro/SSA and anti-La/SSB antibodies**

Anti-Ro/SSA and anti-La/SSB antibodies are directly involved in the pathogenesis of neonatal lupus syndrome (NLS), which is characterized, by transient skin rash, liver and hematological features and congenital heart block (CHB) [51]. This rare syndrome may occur in the offspring of pregnant women with anti-Ro/SSA or/and anti-La/SSB antibodies. It is postulated that maternal anti-Ro/SSA and anti-La/SSB IgG autoantibodies pass through the placenta to the fetal circulation and initiate an immune-mediated damage of the fetal heart and skin. Binding of autoantibodies requires the redistribution of Ro/SSA and La/SSB autoantigens on the surface of myocardial cells [52]. The idiotypic/anti-idiotypic network has also been suggested to contribute to the pathogenesis of NLS [53].

**Anti-carbonic anhydrase II antibodies (anti-CA II)**

Carbonic anhydrase (CA) is an enzyme important for the regulation of acid-base equilibrium. Among 13 active isoenzymes, CA II is a soluble form, found in the cytosol of proximal and distal renal tubular cells. Active immunization of mice with human carbonic anhydrase II leads to the development of SSlike autoimmune sieladenitis [54] while induction of anti-CA II antibodies in a mouse model of SS results in renal tubular acidosis [55]. Anti-CA II antibodies are found in 12.5 to 20.8% of pSS patients [56,57]. Among patients with SS, those with distal renal tubular acidosis have higher levels of anti-CA II antibody than those without renal tubular acidosis [58]. It should be noted that recent studies have also revealed the presence of anti-CA II autoantibodies in IgG4 related disease [59,60].

**Anti-muscarinic type 3 receptor antibodies (anti-M3R)**

Muscarinic receptors (MRs) are acetylcholine receptors coupled to G-proteins. In particular, M3-muscarinic receptor (M3R) mediates parasympathetic cholinergic neurotransmission to salivary and lacrimal glands, bladder, intestine, sweat glands, blood vessels and iris [61]. Over the last 15 years, it has been assumed the presence of autoantibodies against M3R in pSS patients’ sera. Though results of conventional immunological methods aiming to detect the presence of anti-M3R antibodies have been controversial [62–65], functional assays provided the best evidence for their existence and their potential pathogenetic role in pSS [66–68]. Autoantibodies with anti-M3R activity in patients with pSS may contribute to the glandular hypofunction and other autonomic manifestations of these patients, probably by blocking the M3R [69]. Such extraglandular features related to autonomic dysfunction could be overactive bladder [70], gastroesophageal symptoms [71], autonomic cardiovascular neuropathy [72] and Adie pupil [73]. In a recent work, the presence of anti-muscarinic antibodies in pSS patients was associated with higher disease activity score and cytopenias [63]. Finally, Japanese investigators found high prevalence of anti-M3R antibodies in patients with juvenile-onset SS [74].

**Mechanisms Involved in autoantibody production and regulation**

The presence of circulating autoantibodies is a common serological finding in pSS patients. Although their existence indicates a dysregulation of the humoral immune response towards auto-reactivity, little is known about the origin of the autoantibodies and the candidate regulatory mechanisms involved in this process. However, some aspects of these underlying mechanisms have been elucidated by several recent studies.

Firstly, it has been speculated that the autoimmune response is antigen-driven since certain autoantibodies are disease specific, the majority of them is of IgG class and they are directed against multiple epitopes some of which are major, while others are recognized by a minority of autoantibodies [75]. Indeed, the major antigenic regions (i.e. B-cell epitopes) of Ro52 kDa, Ro60 kDa and La molecules have been mapped thoroughly using a variety of epitope mapping procedures [76]. In particular, our group described two major epitopes of La/SSB autoantigen; one immunodominant T-cell/minor B-cell epitope (289–308) and one subdominant T-cell/major B-cell epitope (349–364). Both epitopes exhibit high sensitivity and specificity in detecting anti-La/SSB antibodies [77]. The identification of the B-cell epitopes of these autoantigens also provides useful tools to study the mechanisms involved in the diversification of the autoimmune response in the course of the disease, such as molecular mimicry and epitope spreading. Interestingly, inter- and intra-molecular spreading of epitopes to Ro/La RNP after animals’ immunization with fragments of these autoantigens has been shown [78,79]. Such experiments point out that the autoimmune response is perpetuated and amplified via molecular spreading against the same or other neighbouring autoantigens.

Moreover, it has been indicated that some autoantibodies are produced in the immunopathological lesion. Notably, previous studies have demonstrated that anti-Ro/SSA and anti-La/SSB autoantibodies are enriched in saliva of pSS patients [80–82] while B cells infiltrating the salivary glands contain intracytoplasmic immunoglobulins with anti-Ro/SSA and anti-La/SSB activity [83,84]. Taken together, the affected salivary glands in SS appear to be a major site of autoantibody production.
Based on the above observations, it is assumed that the humoral autoimmune responses are regulated either by factors that are extrinsic to the immune system, the autoantigen being the most important, or factors that are intrinsic to the immune system, such as the local inflammatory environment and the idiotypic/anti-idiotypic network [6]. The way that the latter takes part in the regulation of anti-Ro/SSA and anti-La/SSB autoimmune response will be further analyzed in the following section.

**Anti-Ro/SSA and anti-La/SSB regulation via the idiotypic/anti-idiotypic network**

It has been recently proposed that the anti-idiotypic antibodies, which react with idiotypes of anti-Ro/SSA and anti-La/SSB autoantibodies, have the potential to regulate the autoimmune response [85,86]. The idiotypic/anti-idiotypic interactions within the immune system have become the centre of many studies since 1974, when Jerne firstly formulated the “idiotypic network hypothesis” [87]. According to this theory, under a variety of circumstances, antibodies can themselves be antigenic and cause the production of anti-antibodies, the so-called anti-idiotypic antibodies. Idiotypic and anti-idiotypic antibodies co-exist as part of the normal immune response, interact in a complementary way and maintain the homeostasis of the immune system. Indeed, anti-idiotypic antibodies seem to regulate the autoimmune response by neutralizing idiotypic antibodies or eliciting antibodies with binding characteristics similar to idiotypes [88].

Anti-idiotypic antibodies have been described in healthy individuals as well as in patients with several autoimmune diseases [53,89–92]. It is also noteworthy that some investigators correlated the existence of anti-idiotypic antibodies with the activity of the underlying disease; anti-idiotypic antibodies are found increased in patients in remission from autoimmune disease while they are absent or deficient during active disease [91,93]. The above findings suggest a potential protective role of anti-idiotypic antibodies in the development of autoimmune diseases.

**The idiotypic/anti-idiotypic network of anti-La/SSB autoimmune response**

In the last decade, several studies in our laboratory revealed some interesting aspects of the role that the idiotypic/anti-idiotypic network plays in the regulation of anti-La/SSB autoimmune response. Much effort has been focused on designing complementary epitopes corresponding to major epitopes of La/SSB, investigating the existence and possible regulatory mechanisms of anti-idiotypic response to anti-La/SSB antibodies in Sjögren’s syndrome (SS) and evaluating the role of this network in the pathogenesis and prevention of NLS.

**Complementary epitopes to major epitopes of La/SSB**

The isolation, handling and determination of anti-idiotypic antibodies using the classic techniques, such as isolation of F(ab’)2 fragments, is a challenging task. This limitation arises mainly from the polyclonal autoimmune response, which characterizes the most autoimmune diseases and the fact that some idiotypes are unique to each patient. The assays previously used to detect anti-idiotypic antibodies presented inadequate specificity and sensitivity. Therefore, our group focused on an alternative way of anti-idiotypic antibodies detection [94]. Taken advantage of the detailed knowledge of the major La/SSB epitopes, we prepared complementary epitopes anticipated to be recognized by anti-idiotypic antibodies, as proposed by the “molecular recognition” theory (described by Blalock [95]). There are previous experimental data, which suggest that these complementary peptides have the ability of generating and detecting interacting pairs of idiotypic and anti-idiotypic antibodies [96].

**Regulatory implications for Sjögren’s syndrome**

Autoantibodies to La/SSB are found in sera of patients with SS. In our first work on anti-idiotypic antibodies [94], we sought to examine the existence and the role of the idiotypic/anti-idiotypic network on the regulation of anti-La/SSB response in SS by using complementary epitopes to the major epitopes of La/SSB. That study uncovered the presence of an active anti-idiotypic response targeting anti-La/SSB antibodies in sera of pSS and SLE patients. A major achievement of that work was the development of a specific procedure in order to detect hidden anti-La/SSB antibodies masked by anti-idiotypic antibodies. The application of this method to anti-Ro/SSA(+) anti-La/SSB(−) sera indicated that all anti-Ro/SSA(+) autoimmune sera also contain also anti-La/SSB antibodies.

To further investigate the potential of the complementary epitopes to serve as a triggering factor for the production of anti-La/SSB autoantibodies, immunization of the non-autoimmune mice (Balb/c) with the major epitopes of La/SSB and their complementary peptides was performed [97,98]. Immunization with either epitope or complementary epitope was found to result in the production of antibodies against both peptides, associated also with the induction of strong T-cell responses. Thus, the complementary epitopes of La/SSB may be involved in the initiation of the autoimmune response against La/SSB autoantigen. These results were confirmed by further studies in other autoantibodies. In fact, autoimmunity to proteinase-3 (PR3), the major autoantigen in Wegener’s granulomatosis, can be initiated through an immune response against a peptide that is complementary to this autoantigen [99,100].
Pathogenetic and preventive implications for neonatal lupus syndrome

Since the appropriate tools and methods to detect the anti-idiotypic antibodies had been already developed, the evaluation of the impact of the idiotypic/anti-idiotypic network on an exemplary model disease was required. Among the systemic autoimmune diseases, NLS appeared to be the ideal candidate for studying the idiotypic/anti-idiotypic response as: it is conceived as a model of passively acquired systemic autoimmune disease, non-organ specific antibodies (i.e. maternal anti-Ro/SSA and anti-La/SSB antibodies) are strongly implicated in its pathogenicity and most importantly, it is characterized by a defined time of clinical appearance and quite expected way of evolution.

Stea et al. in our laboratory [53] tested blindly the sera of 63 pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies by using Elisa against synthetic peptides corresponding to major epitopes and complementary epitopes of La/SSB. Pregnant women were divided into three subgroups: mothers carrying a child with NLS (group A), mothers carrying a healthy child but also having a previous child with NLS (group B) and mothers giving birth to a healthy child without history of a child with NLS (group C). This study demonstrated for the first time the existence of an active network of idiotypic/anti-idiotypic antibodies directed to the major B-cell epitope of La/SSB, being in association with the development of NLS. Indeed, it was disclosed that sera from mothers of group C exhibited higher anti-idiotypic activity compared with sera from mothers of groups A and B. With regard to the sera without any evident idiotypic/anti-idiotypic response to the major B-cell epitope (349–364), recovery of the hidden anti-peptide activity was carried out by specific blocking of the anti-idiotypic antibodies. This analysis revealed the presence of hidden antibodies in the sera of mothers with healthy children. These data support the notion that anti-idiotypic antibodies to autoantibodies against the major epitope of La/SSB may constitute a protective factor for the fetus, probably by forming complexes with the pathogenetic antibodies and consequently prohibiting their binding to the fetal tissues and tissue destruction. Moreover, testing for these anti-idiotypic responses may be used as a serological marker of low-risk pregnancies.

CHB is undoubtedly the most serious manifestation of NLS since it may result in permanent and life-threatening damage to the fetal heart. The incidence of CHB in mothers with anti-Ro/SSA and/or anti-La/SSB antibodies is approximately 1 to 2% [101,102]. However, the recurrence rate in subsequent pregnancies following the birth of a child with NLS is almost 18% [103–105]. Treatment of CHB in pregnant women remains challenging. As the most of the immunomodulatory agents are harmful for the developing fetus, clinical investigators wondered whether the administration of Intravenous Immunoglobulin (IVIG) could prevent the development of CHB in the fetuses of high-risk pregnant women (i.e. women who had already given birth to at least one child with CHB). It is stated that IVIG may prevent tissue damage through some suggested mechanisms: by increasing the elimination of maternal anti-Ro/SSA and anti-La/SSB antibodies, by reducing the transplacental transport of antibodies and by modulating the inhibitory signals on macrophages, which may result in reduction of the inflammatory response and the consequent fibrosis of the fetal heart [106–108]. Two recently published multicenter studies concluded that IVIG treatment at low doses is not effective enough to prevent the recurrence of CHB in fetuses of high-risk mothers [109,110].

In order to contribute to the interpretation of the results of two previous studies, we attempted to evaluate the effects of such IVIG therapy on the idiotypic/anti-idiotypic network of anti-La/SSB antibodies [111]. Sera from 16 anti-Ro/SSA and anti-La/SSB positive pregnant women who were enrolled in the Preventive IVIG Therapy for Congenital Heart Block (PITCH) study were tested blindly for alterations of their idiotypic/anti-idiotypic activity against the major B-cell epitope (349–364aa) of La/SSB after the administration of IVIG. It was shown that IVIG treatment was accompanied by increase of the anti-idiotypic response and attenuation of the idiotypic response in the majority of tested sera. In addition, the idiotypic/anti-idiotypic ratio of antibodies against the major epitope of La/SSB after IVIG administration appeared to be significantly higher in mothers whose offspring presented NLS. This finding suggested the contribution of an inadequate anti-idiotypic response in the pathogenesis of NLS. Furthermore, all IVIG preparations were also examined for idiotypic/anti-idiotypic antibody activity. This procedure was carried out in order to clarify if the increase of the anti-idiotypic activity after IVIG treatment was due to exogenous addition of anti-idiotypic antibodies contained in the IVIG preparation. It was demonstrated that IVIG from batches administered to mothers who gave birth to a child with NLS exhibited higher idiotypic/anti-idiotypic ratio compared to that given to mothers who gave birth to a healthy child. That was the first study in humans which indicated that IVIG influences the idiotypic/anti-idiotypic network of a specific pathogenic autoantibody and that the idiotypic/anti-idiotypic ratio in both the IVIG preparation and the maternal serum may be associated with the efficacy of IVIG treatment for the prevention of recurrent NLS.

Disclosure of interest: the authors declare that they have no conflicts of interest concerning this article.
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